THE PREPARATION OF
SOME MERCAPTOINDOLES

by

ROBERT JOHN CUSHLEY

B. Sc.

1959

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THE UNIVERSITY OF ALBERTA

THE PREPARATION OF SOME MERCAPTOINDOLES

A DISSERTATION
SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF MASTER OF SCIENCE

FACULTY OF ARTS AND SCIENCE

DEPARTMENT OF CHEMISTRY

by

ROBERT JOHN CUSHLEY, B. Sc.

EDMONTON, ALBERTA
September 1, 1959

ACKNOWLEDGEMENT

The author wishes to express his sincere thanks and appreciation to Dr. R. K. Brown, whose unfailing encouragement and advice made this work possible.

He also wishes to thank Canadian Industries Limited for their generous fellowship, and the National Cancer Institute of Canada for financial support during the summer.

THE PREPARATION OF SOME MERCAPTOINDOLES

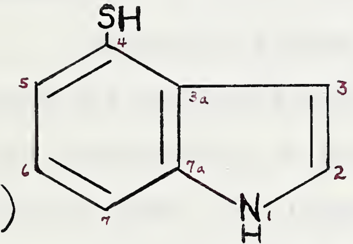
INTRODUCTION

In a previous attempt to synthesize mercaptoindoles in this laboratory the 5- and 6-mercaptoindoles were obtained (1).

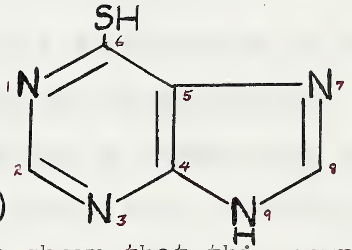
It was thought desirable to prepare the remaining unknown indolyl mercaptans, the 7-, and especially the 4-mercaptoindole in order that they might be available for physiological testing.

The interest in 4-mercaptoindole (A) stems from the recent successful application of the structurally analagous 6-mercaptopurine (B) to the treatment of leukemia.

(A)



(B)



Various workers (2,3) have shown that this compound is antagonistic to certain connective tissue cancers in mice and produces leukopenia, for a short while at least, in leukemia patients who have developed a resistance towards ACTH and cortisone. It was thought that 4-mercaptoindole might exhibit some anticarcinogenic properties because of its close resemblance to the chemotherapeutic 6-mercaptopurine.

GENERAL DISCUSSION

Examination of the literature and previous attempts (1) have shown that a simple and direct method for the introduction of a thiol group into the indole nucleus is difficult if not impossible. Hence, it was felt that the sulfur moiety should be suitably placed in an aromatic structure which could then be induced to form the indole.

A number of methods for the preparation of indoles are available.

Stevens (4) formed indole by condensation of o-aminophenylacetaldehyde; actually an extension of his aldehyde synthesis.

Tyson (5) formed indoles by a modification of the Madelung (6) synthesis which involves an intramolecular Claisen condensation of acyl derivatives of o-toluidine in the presence of base. He formed 79% of indole from o-formotoluidide using potassium tertiary butoxide as the condensing agent.

Reminiscent of the Madelung synthesis is the one devised by Gluud (7). Heating o-aldehydophenylglycine with sodium acetate - acetic anhydride is stated to yield 80% of indole.

Possibly the most widely applicable method for the preparation of indoles is that discovered by Emil Fischer (8). Fischer's synthesis involves the cyclization of phenyl hydrazones of alkyl or alkaryl ketones, aldehydes or keto-acids. The cyclization has been carried out with a large variety of

cyclizing agents, usually acidic, although a recent paper indicates that basic conditions also permit cyclization (9). Indole is not available by direct application of this method but can be prepared from decarboxylation of 2-carboxyindole obtained by the cyclization of the phenyl hydrazone of pyruvic acid. Previously, Brown and Kutney (10), in this laboratory, attempted to produce mercaptoindoles by this method. They replaced the chlorine atom with the mercapto group by treatment of p-nitrochlorobenzene with sodium sulfide. The nitro group was also reduced to the amine in this step, but they were unable to obtain a pure phenyl hydrazine in the next step, so this route was abandoned.

The Japp-Klingemann reaction (11) has proved to be a valuable adjunct to the Fischer method since it provides a method of preparing the phenyl hydrazones by reaction of phenyl diazonium chloride and the sodium salts of either β-keto acids or their esters.

There are also several methods which involve cyclization of two carbon chains in o-aminophenyl compounds (12,13). Ek and Witkop (14) were thus able to synthesize 5- and 7-benzyloxyindoles from 3- and 5-benzyloxy-o,ω-dinitrostyrenes by the Nenitzescu-Van der Lee synthesis. Perhaps the best known example of this type is the Reissert synthesis (15). Reissert prepared indole by cyclizing o-nitrophenylpyruvic acid in zinc and acetic acid. Shorygin and Polyakova (16) state that, in their study of synthetic preparations of indoles, the Reissert method gave optimum results.

There are also several methods given for the preparation of mercapto compounds.

Treatment of diazonium salts with potassium ethyl xanthate produces xanthogenic esters which may be hydrolized with alkali to yield thiols (17). Lithium aluminum hydride reduction of the xanthogenic esters has improved the thiol yields considerably (18) but requires isolation of the xanthogenic ester and is quite expensive.

Thiols have been prepared from the action sodium or potassium hydrogen sulfide displacing the halogen of a suitable chloro or bromo compound. Schaeffer, et al (19(a), (b)) synthesized ribonucleosides of 2- and 6- mercaptopurines by this method.

The reaction between sufficiently reactive halogen compounds and thiourea also produces thiols in good yield when the resulting thiouronium salt is hydrolized by base. Phillips and Shapiro (20) synthesized 2-mercaptopyridine from 2-bromopyridine using this method.

Aryl sulfonyl chlorides have been reduced with zinc dust and sulfuric acid, tin and hydrochloric acid, or lithium aluminum hydride to the corresponding thiols. Thus, Adams and Marvel (21) produced thiophenol by the reduction of benzene sulfonyl chloride with zinc dust and sulfuric acid at 0-5°. Similarly, Marvel and Caesar (29) prepared 4-mercaptotoluene in 50% yield using p-toluenesulfonyl chloride and lithium aluminum hydride.

Other methods for the preparation of mercaptans are the reaction of phenols with phosphorous pentasulfide (23)

and the reaction of sulfur on Grignard reagents. Oddo and Mingoia (24) prepared 3-mercaptoindole by the latter method.

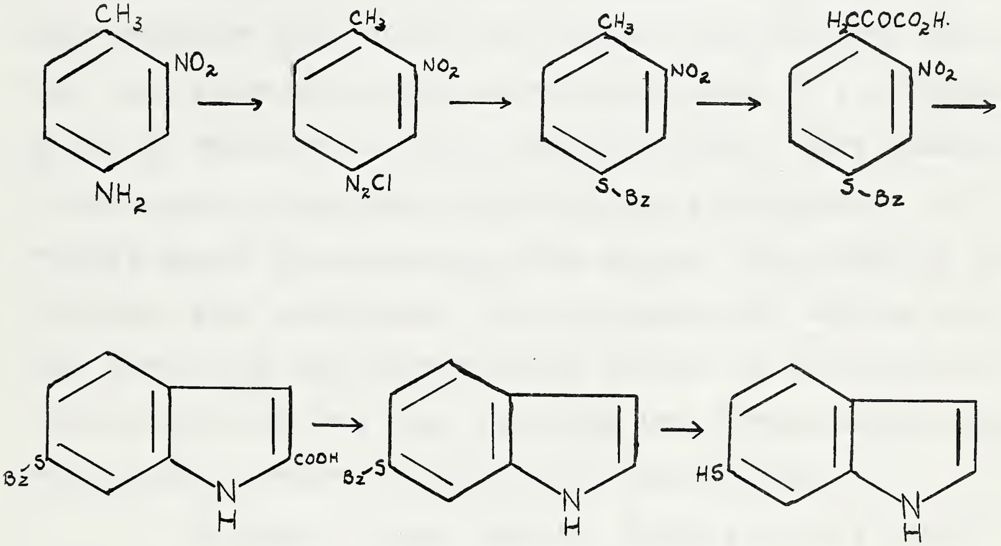
A number of the above methods have been attempted in this laboratory in an effort to produce 4-mercaptoindole and the remaining, unknown mercaptoindoles.

Brown and Kutney (10) attempted to produce mercaptoindoles by reduction of the appropriate nitrosulfonyl chlorides. However, all their efforts met with failure..

Continuing this work V. B. Haarstad (1), also in this laboratory, attempted to replace a bromine atom, attached to the indole nucleus by a thio group, using sodium or potassium hydrogen sulfide or thiourea. 4- and 6-Bromoindoles were prepared by the method of Plieninger (25), by condensation of the appropriate o-nitrotoluene with diethyl oxalate, reduction of the resulting phenylpyruvic acid and decarboxylation of the 2-carboxyindole. The 4-bromoindole so prepared was then treated with thiourea or potassium hydrogen sulfide in various solvents but no mercaptoindoles were isolated.

The route finally found which would yield the desired products, involved introducing the mercapto group into the ring before cyclization. Thus, 2-nitro-4-aminotoluene was diazotized, converted to the xanthogenic ester, followed by hydrolysis and immediate benzylation to protect from oxidation to the disulfide. Then the 2-nitro-4-benzylmercaptotoluene was condensed with diethyloxalate in the presence of sodium ethoxide. The resulting phenylpyruvic acid was then

reduced with ferrous sulfate to 6-benzylmercaptoindole-2-carboxylic acid. This was decarboxylated in quinoline with a copper chromite-barium chromite catalyst. The final step in the preparation of 6-mercaptoindole was cleavage of the benzylthio ether to remove the benzyl group. This was accomplished using sodium in liquid ammonia. Du Vigneaud, et al (26) prepared cysteine by debenzylation of S-benzyl cysteine in this manner. The following scheme illustrates the reaction sequence:



The 5-isomer was prepared by essentially the same route.

In view of the results obtained in producing the 5- and 6-mercaptoindoles an analogous procedure was proposed for the synthesis of the 4- and 7-mercaptoindoles, requiring the preparation of 3- and 6-amino-2-nitrotoluenes.

En route to the 4-mercaptoindole, the problem of synthesizing 2-nitro-6-aminotoluene arose. Parkes and

Farthing (27) prepared 2-nitro-6-aminotoluene via the reduction of 2,4,6-trinitrotoluene to yield 2,4-diamino-6-nitrotoluene by treating it with a solution of ethyl alcohol saturated with ammonia and hydrogen sulfide. The product was monoacetylated at the 2-amino group and deamination yielded 2-nitro-6-acetaminotoluene. The 2-nitro-6-aminotoluene thus produced melted at 90°.

However, a later article by Foster, Rosicky and Niemann (28) questioned Parkes and Farthing's assignment of the acetyl group to the 2-amino position. By following the same procedure they arrived at 2-nitro-4-aminotoluene (m.p.78°). They then prepared 2-nitro-4-acetaminotoluene by a different method of reduction of 2,4,6-trinitrotoluene. They reduced the p-nitro group, acetylated the resulting p-amino group, and reduced one of the remaining nitro groups. The compound they obtained, when acetylated, did not depress the melting point when mixed with the monoacetylated product of 2,4-diamino-6-nitrotoluene and they thus concluded that Parkes and Farthing had actually prepared 2-nitro-4-acetaminotoluene.

Because of these results, Foster, et al's method of stepwise reduction was followed. 2,4,6-Trinitrotoluene was reduced in ethanol with hydrogen sulfide and ammonium hydroxide to the hydroxylamine. The separation of the hydroxylamine from the sulfur mass proved extremely difficult since the warm solution gave a precipitate which was almost unfilterable. The hydroxylamine was then reduced with concentrated hydrochloric acid and potassium iodide to 2,6-dinitro-4-aminotoluene

in 30% yield. The product was then dissolved in concentrated hydrochloric acid in preparation for deamination. A large excess of strong acid was necessary to dissolve the amine, doubtless due to the acidifying effect of the two nitro groups meta to the amine. Deamination was carried out according to the method of Kornblum (29). The amine was diazotized and added to 50% hypophosphorus acid at 0°. There was recovered very little 2,6-dinitrotoluene. The diazotization procedure was altered in an attempt to improve the yield. Hodgeson's method for diazotizing hindered amines was used (30). The pink diazonium sulfate was isolated, and added directly to the hypophosphorus acid but no improvement in yield was noticed. Using ethanol as the deaminating agent, or hypophosphorus acid as both the diazotizing acid and deaminating agent gave similarly poor results. The small amount of crude 2,6-dinitrotoluene produced would not reduce satisfactorily with ammonium sulfide (31) or by electrolytic means (32).

It was therefore decided to arrive at the 2-nitro-6-mercaptoindole via the replacement of a halogen with potassium hydrogen sulfide. Previously, V. Haarstad (1), in this laboratory, had treated 2-nitro-6-bromotoluene with a saturated solution of potassium hydrogen sulfide in refluxing methanol and in secondary butanol but without success. However, it was suspected that due to the slow rate of displacement of the 6-bromine atom, the volatile hydrogen sulfide might be lost gradually from the reaction by the following equilibrium:

$NaSH + ROH \rightleftarrows RONa + H_2S$

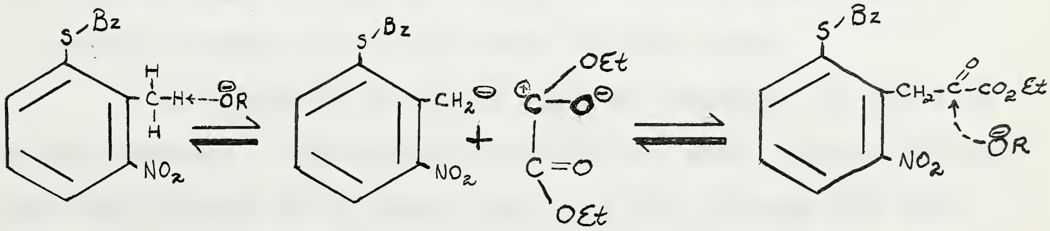
Since precautions were not taken by V. Haarstad to avoid this, the experiments were repeated in a refluxing 1 normal solution of alcoholic sodium hydroxide continually saturated with hydrogen sulfide but, after eighteen hours, no mercaptotoluene was isolated.

At this time an article by Schaeffer and Thomas (19b) pointed out that sodium benzylmercaptide is a much more reactive nucleophylic reagent than sodium hydrogen sulfide. Therefore, 2-nitro-6-bromotoluene was allowed to react with two equivalents of a 1 Molar solution of sodium benzylmercaptide in methanol, and 2-nitro-6-benzylmercaptotoluene was isolated in 20% yield. The application of Johnson, Holum, and Montgomery's (33) improved procedure, using dimethyl formamide as the solvent, raised the yield of 2-nitro-6-benzylmercaptotoluene to 40%. That it was not 2-nitro-5-benzylmercaptotoluene, which could conceivably be prepared under these conditions, was shown by physical properties and infrared studies.

There have been few references concerning the preparation of benzyl mercaptan. Marcher (34) first prepared benzyl mercaptan in 1865 by the action of benzyl chloride on alcoholic potassium hydrogen sulfide. Rodinov (35) prepared benzyl mercaptan by the action of sodium thiosulfate on benzyl chloride, while Frank and Smith (36) used benzyl alcohol and thiourea to produce the corresponding thio alcohol. Zinner (37), exercising meticulous care and using an atmosphere of nitrogen or hydrogen sulfide gas, devised a set of conditions which led to 85% yield of benzyl mercaptan by the reaction of benzyl bromide with alcoholic potassium hydrogen sulfide.

However, we adapted the method of Urquhart (38) to the preparation of benzyl mercaptan since isolation and purification proved easier. Using slightly longer reaction times, yields to 80% of mercaptan were realized by the reaction of benzyl chloride with thiourea.

The next step in the Reissert indole synthesis involved condensation of the toluene with diethyl oxalate in the presence of sodium ethoxide to form the phenyl pyruvic acid. However, when 2-nitro-6-benzylmercaptotoluene was subjected to this reaction, the characteristic red color of the enolate ion of the pyruvic ester in basic solution formed with difficulty and the solution did not become intensely wine red and thick as is usual in most cases. Steric hindrance was believed responsible for this since the methyl group was butressed on the one hand by a nitro group and on the other hand by a benzylmercapto group. Also since reaction had taken place and formed the red enolate ion, and since hydrolysis yielded only traces of product, it was thought that the reverse reaction was taking place much more readily than the forward reaction.



It was hoped that, by increasing the basic strength of the catalyst,the steric hindrance might be overcome. Since potassium tertiary butoxide has been shown to be a better base for hindered compounds containing active hydrogen (39) than sodium ethoxide, the reaction was tried in the presence of this base. It was also hoped that the reverse reaction would be cut down since the attack at the carbonyl of the phenyl pyruvic ester would be lessened by the bulkier nature of the tertiary butoxide ion, assuming that such an attack actually occurs to "reverse" the reaction. To assure optimum conditions for the completion of the reaction a two to one molar excess of both alkoxide and of diethyl oxalate to toluene was used under anhydrous conditions. Reaction with sodium amide in ether did not improve the yields over potassium tertiary butoxide (40). The isolation of the acid had to be carried out as quickly as possible, and the acid used immediately for the next step, since the reaction tended to form the toluene even after hydrolysis of the ester had taken place. Indeed, R. K. Brown in this laboratory had shown that even 2-nitro-4-benzylmercaptophenylpyruvic acid was converted to the toluene (41) if left dissolved in ethanol (from which it is usually crystallized) for three to four weeks.

Best results depended upon the sequence of addition of the reagents. The diethyl oxalate was added slowly to the base and stirred for a short time, and the toluene was then added. The addition of diethyl oxalate to the base produced a precipitate of white flakes which could be removed by

filtration.. The supernatant liquid was found to bring about condensation while the potassium containing precipitate would not. Work is continuing on the nature of the basic species which acts as catalyst for the reaction. It will be noted that the sequence of addition is in contrast with that generally associated with condensation reactions involving carbanions (40), i.e., primary mixing of base with toluene to affect carbanion formation. When this sequence of addition occurred, no reaction took place.

When the ester was hydrolized the resulting phenyl pyruvic acid separated as an oil and did not crystallize. Since distillation probably would have led to decomposition, it was used without further purification. That it actually was the phenyl pyruvic acid was shown by the positive tests which it gave for this structure, i.e: green solution with alcoholic ferric chloride and a red solution with sodium hydroxide.

The phenyl pyruvic acid was reduced to the carboxyindole by means of ferrous sulfate and ammonium hydroxide. The carboxyindole was isolated by tedious repeated extraction with hot concentrated ammonium hydroxide from the ferric hydroxide sludge. The carboxylic acid was carefully freed from sulfate since Rydon and Tweddle have shown that sulfate inhibits the decarboxylation of carboxyindole (42). Decarboxylation was accomplished by refluxing in quinoline with a copper chromite catalyst. The resulting 4-benzylmercaptoindole was isolated as an oil. The oil could not be induced to crystallize

but since 4-chloroindole is an oil while 5-, 6-, and 7-chloroindoles are solids, the same phenomenum might apply in the case of the 4-benzylmercaptoindole versus the 5-, 6-, and 7-isomer. Attempts at sublimation led to decomposition of the product, hence distillation was not attempted. However, infrared studies showed very good evidence of decarboxylation to 4-benzylmercaptoindole. Also the product gave a positive Erlich's test (43) while the 2-carboxyindole did not, thus showing a free 2 position.

The final step in the preparation of 4-mercaptoindole was cleavage of the benzylthio ether. Hughes and Thompson (44) state that alkali cleavage of the thio ethers is accomplished as easily as cleavage of oxygen ethers with acid. This is no doubt due to the ability of sulfur to accommodate the basic electrons in its outer shell thus giving rise to R_2S^- or $R_2S^=$ species which then dissociate:

$$R_2S + 2Na \rightarrow RS^- + R^- + 2Na^+$$

$$R_2S + 2Na + NH_3 \rightarrow RSNa + RH + NaNH_2$$

Since du Vigneaud, et al, (26) prepared cystine by debenzylation of S-benzyl cysteine with sodium in liquid ammonia, his method was adopted. A base soluble compound, which smelled like burnt rubber, was isolated which was purified by reprecipitation with acid. The compound solidified below 0-5°C but remained an oil at room temperature. Molecular distillation of the oil was accompanied by much

charring but a fawn colored solid was isolated melting at 32-34°C. Infrared data indicated the indole nucleus was in tact and the compound has been tentatively identified as 4-mercaptoindole.

Regarding the 7-isomer, the preparation of 2-nitro-3-aminotoluene by the method of Geerling and Wibaut (45) was first attempted.. A sample of the methyl ester of m-toluic acid, kindly donated by Hercules Powder Co., was hydrolized with sodium ethoxide. The acid thus obtained was nitrated according to the method of Muller (46) to yield 2-nitro-m-toluic acid. The latter was converted to the amide and this subjected to a Hofmann degradation using the Hoogewerf and van Dorp modification (47). However, conversion of the amide to the amine gave very low yields. Because of the electron withdrawing effect of the o-nitro group, hydrolysis to the carboxylic acid is facilitated and rearrangement to the amine is seriously affected (48). Since rearrangement possesses a higher temperature coefficient than hydrolysis, the degradation was conducted at reflux conditions but still no improvement in yield was noticed.

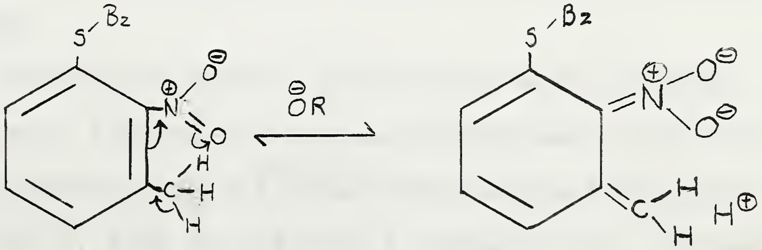
However, the application of the Schmidt reaction to the 2-nitro-m-toluic acid gave 50% of the amine in a single step (49). On the other hand, Geerling's method involves three steps, one producing the heat sensitive acid chloride which led to an explosion in one case.

The amine was converted to the acid salt, diazotized and xanthated (17). The resulting xanthogenic ester was hydrolized with potassium hydroxide and immediately benzylated to protect the mercapto group. After isolation, the crude

2-nitro-3-benzylmercaptotoluene was vacuum distilled but the yield was extremely small. Further examination showed that the amine was soluble in hot water and formed the acid salt with difficulty. When care was taken to insure that all of the amine was converted to the salt in a large excess of hot concentrated acid, and the experiment repeated, the yield was improved. However, due to losses by oxidation, incomplete hydrolysis, and large decomposition during the final distillation, the yield remained low at 19%.

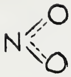
All attempts at condensing the 2-nitro-3-benzylmercaptotoluene failed. Catalysts of sodium ethoxide, potassium ethoxide, tertiary butoxide, sodium amide in ether and sodium amide in liquid ammonia (50) were used in various solvents but no phenylpyruvic acid was isolated from the reaction.

Fischer-Hirschfelder atom models of the 2-nitro-3-benzylmercaptotoluene revealed large steric interaction between the central nitro group and the buttressing o-methyl and o-benzylmercapto groups. It was thought that the buttressing effect of these two groups provided too much strain for the nitro group to become coplanar with the ring and thus activate the methyl group sufficiently for carbanion formation:



Infrared studies of the various toluenes bear this out. Table I shows the nitro peaks for the asymmetric stretching vibrations of the nitro groups of the various toluenes.

TABLE I

Infrared  Stretching Bands

Calibrated by polystyrene - 6.238 microns

Compound	Assignment-microns	
	Asymmetric	Symmetric
o-nitrotoluene	6.54	7.40
2-nitro-4-benzylmercaptotoluene	6.53	7.40
2-nitro-6-benzylmercaptotoluene	6.52	7.37
2-nitro-6-benzylmercaptotoluene	6.50	7.29
nitromethane	6.38	7.18

It will be seen that as the nitro group becomes increasingly hindered sterically, the nitro peaks are shifted towards the lower wavelengths indicating greater aliphatic nature, and hence possess less tendency to activate the o-methyl group.

Ultraviolet studies proved even more striking: o-nitrotoluene, 2-nitro-4-benzylmercaptotoluene, and 2-nitro-6-benzylmercaptotoluene all showed well-defined absorption peaks at 2530 Å, 2525 Å, and 2510 Å respectively; nitromethane

absorbed weakly and gave a plateau at 2800 Å; while 2-nitro-6-benzylmercaptotoluene formed plateaus at 2850 Å and at 2540 Å, again indicating the considerable aliphatic character of the nitro group.

EXPERIMENTAL

2-Nitro-6-bromotoluene - o-Nitrotoluene was brominated according to the method of Gluud (51). The 2-nitro-6-bromotoluene was separated from the 2-nitro-4-bromotoluene by fractionation under reduced pressure with a meter length column packed with metal. The 2-nitro-6-bromotoluene distilled first and came over slowly. The product solidified in the receiver and was recrystallized from ethanol containing a little water. From 489 g. of o-nitrotoluene there was obtained 200 g. (26%) of 2-nitro-6-bromotoluene, b.p. 108-110° (3.3 mm.), m.p. 41-42 uncorr., (lit. 42°).

Benzyl Mercaptan - Benzyl mercaptan was prepared by the method of Urquhart (38). Benzyl chloride (63.3 g., 0.5 moles) and thiourea (38.6 g., 0.5 moles) was added to 250 ml. of 95% ethanol. The mixture was heated with stirring till the substances just dissolved. The solution was kept at this temperature and continually stirred 14 hours. The mixture was cooled and 30 g. of sodium hydroxide (0.75 moles) in 300 ml. of water was added. The solution was again heated until the precipitate just dissolved and kept at this temperature for 6 hours. The solution was cooled and acidified with sulfuric acid. A layer of mercaptan separated. The aqueous layer was extracted with ether. The ethereal washings were added to the oil and this was washed twice with water and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and the oil was distilled, yielding 49 g. (79%) of

benzyl mercaptan, b.p. 187° (700 mm.). All steps were carried out under an atmosphere of nitrogen and the product used immediately for the next step.

2-Nitro-6-benzylmercaptotoluene - 2-Nitro-6-bromotoluene (55 g., 0.25 moles) was dissolved in 50 ml. of dimethylformamide. Powdered potassium carbonate (38.8 g., 0.28 moles) was added with stirring. Benzyl mercaptan (31.3 g., 0.25 moles) was added all at once. The reaction was kept under a blanket of nitrogen and heated for 4 hours at 50-55°, and then stirred at room temperature 14 hours. The solution was added to an equal volume of water and cooled to 0°. The resulting crude yellow solid was triturated with dilute sodium hydroxide and with water. It was then recrystallized several times from ethanol yielding 25.9 g. (40%) of yellow needles, m.p. 102-103°.

Anal. Calculated for $C_{14}H_{13}O_2NS$: S, 12.37.

Found: S, 12.32, 12.15.

2-Nitro-6-benzylmercaptophenylpyruvic Acid - Potassium (2.1 g., 0.054 moles) was dissolved in 150 ml. of anhydrous tertiary butyl alcohol and cooled to 10°. Diethyl oxalate (7.8 g. 0.054 moles) was added dropwise to the cooled solution. A white precipitate formed and the solution was stirred for 1 minute. An ethereal solution of 2-nitro-6-benzylmercaptotoluene (6.9 g., 0.027 moles) was added slowly. The solution was refluxed for 16 hours. A wine-red color was immediately imparted to the solution which became more intense, and the solution became thicker as the reaction progressed. The solution was added to an equal volume of ice-water and stirred

at 0° for 2 hours. The oil which separated was extracted with warm dilute sodium hydroxide till the basic extractions were only slightly red. These were combined with the original aqueous solution and extracted twice with ether. Starting material to the extent of 3 g. was recovered from the ether washings. The oil was redissolved in ammonium hydroxide and reprecipitated with concentrated hydrochloric acid. The oil was then extracted with ether, the ether dried over anhydrous sodium sulfate, and removed under vacuum. There remained 3.9 g. (39%) of a dark orange oil which was used immediately for the next reaction.

2-Carboxy-4-benzylmercaptoindole - The method of Blaikie and Perkin (52) was used. To a solution of 2-nitro-6-benzylmercaptophenylpyruvic acid (3.5 g., 0.011 moles) dissolved in concentrated ammonium hydroxide was added 50 g. of ferrous sulfate heptahydrate in 125 ml. of water. Reduction was instantaneous and the black mixture was heated on the steam bath for 3 hours. The hot solution was filtered and the black ferric hydroxide sludge was tediously extracted with hot concentrated ammonium hydroxide until the extracts did not give a precipitate upon acidification. The solution was acidified to Congo Red with concentrated hydrochloric acid, cooled well in ice and filtered. The light brown precipitate was washed well with water and dissolved in ether. It was washed with a very dilute solution containing some barium chloride to remove sulfate, and then twice with water. The ethereal solution was dried over anhydrous sodium sulfate and the ether was removed. The solid

remaining was extracted repeatedly with hot, concentrated ammonium hydroxide, acidified, cooled, washed with water, and dried, yielding 1.6 g. (53%) of 2-carboxy-4-benzylmercaptoindole m.p. 172-173°.

Anal. Calculated for $C_{16}H_{13}O_2NS$: S, 11.35.

Found: S, 11.31.

4-Benzylmercaptoindole - 2-Carboxy-4-benzylmercaptoindole (1 g., 0.0035 moles) and 0.25 g. of copper chromite-barium chromite catalyst (53) were refluxed for 16 hours in 50 ml. of redistilled synthetic quinoline. The cooled quinoline solution was acidified with 3N. hydrochloric acid and extracted five times with ether. The ether extracts were combined, filtered to remove suspended catalyst, washed once with 3 N. hydrochloric acid, twice with saturated aqueous sodium bicarbonate, twice with water, and dried over anhydrous sodium sulfate. The ether was removed and the oil remaining was extracted with hot ethanol, treated with norite, and reduced in volume and allowed to cool. However, no crystals appeared and the ethanol was removed under reduced pressure. Crystallization was attempted with various solvents but none proved successful. Sublimation led to decomposition of the product and distillation was abandoned for this reason. Chromatography with an alumina column was then attempted. The first elution with benzene yielded a yellow oil (0.284 g., 34%) which gave a positive Erlich's test. This oil could not be induced to crystallize, and was subsequently used for the next reaction.

4-Mercaptoindole (26) - Liquid ammonia (10 ml.) was placed in a 20 x 150 mm. test-tube, with side-arm, supported in a Dewar flask by means of a cork. To this was added (130 mg., 0.54 mmoles) of 4-benzylmercaptoindole followed by small pieces of sodium metal stirred into the solution until the deep blue color persisted for 5-10 minutes. Excess sodium was destroyed by adding ammonium iodide until the blue color disappeared. The test-tube was removed from the Dewar and the ammonia was boiled off under a blanket of nitrogen. Residual ammonia was removed by alternately evacuating the test tube and flushing it with nitrogen. Freshly boild and cooled, distilled water (15 ml.) was added to the residue and the solution was removed from the test-tube. The solution was acidified with 3 N. hydrochloric acid and immediately placed in a sealed flask under nitrogen. An oil separated when the flask was cooled and several reprecipitations from dilute sodium hydroxide solution with 3 N. hydrochloric acid failed to yield a crystalline product. The brown oil was dissolved in ether, washed twice with freshly boiled and cooled distilled water, and dried over anhydrous sodium sulfate. After the ether was removed under reduced pressure, there remained 48.2 mg. (59.5%) of a brown oil which smelled of burnt rubber. Micro-distillation of this oil led largely to decomposition but there was recovered some oil, b.p. 180-185° bath temperature(9 mm.) which, when dissolved in ether and then the ether evaporated under a stream of purified nitrogen, yielded fawn micro-crystals, m.p.

32-33°. The "mercaptan" was immediately stored in a sealed container under nitrogen. Anal. of solid mp 32-33°. Found. S = 3.60 ; 3.75 % S ∴ isn't 4-mercapto indole.

Anal. of brown oil. Calculated for C_8H_7NS : S, 21.48.

Found: S, 20.88; 20.69

m-Toluic Acid - A sample of commercial methyl m-toluate (110 g., 0.73 moles) which contained 93% methyl m-toluate and 7% methyl p-toluate, kindly donated by the Hercules Powder Company, was stirred for 15 hours with a solution of 32 g. sodium (1.39 moles) in 1000 ml. of absolute ethanol to which 100 ml. of water had been added. The solution was diluted to 3-4 times its volume with ice water. Concentrated hydrochloric acid was added until precipitation was complete and the mixture was digested in an ice bath for 5 hours. The solid was filtered, washed with water, dissolved in 10% sodium hydroxide and reprecipitated with concentrated hydrochloric acid. The acid was crystallized several times from ethanol-water. The yield was 100 g. (90%), m.p. 108-109° uncorr., (lit. 111°).

2-Nitro-m-toluic Acid - The method of Muller (46) was employed to nitrate m-toluic acid. From 50 g. of m-toluic acid (0.37 moles) there was recovered 33.3 g. (50%) of 2-nitro-m-toluic acid, m.p. 213-218° uncorr., (lit. 219-220°).

2-Nitro-3-aminotoluene - 2-Nitro-m-toluic acid was converted to the amine via the Schmidt reaction (50). Finely powdered 2-nitro-m-toluic acid (28 g., 0.15 moles) was dissolved by heat in 200 ml. of chloroform. Concentrated sulfuric acid (84 ml., d., 1.84) was added with stirring. Powdered sodium azide

(11.2 g., 0.17 moles) was added slowly to the solution. The temperature was maintained at 45° for 4 hours, while maintaining vigorous stirring, until gas was no longer evolved (about 4 hours). The solution was added to 3 times its volume of ice water and neutralized by slow addition of 10% sodium hydroxide. The temperature was kept below 10°. The mixture was then distilled with steam yielding orange-red crystals of 2-nitro-3-aminotoluene m.p. 105-106° uncorr., (lit. - 108°).

2-Nitro-3-benzylmercaptotoluene - The method of Bennett and Berry (54) was employed to convert the amino group to the thiol. To a hot solution of 100 ml. of concentrated hydrochloric acid in 450 ml. of water was added 21 g. of powdered 2-nitro-3-aminotoluene (0.138 moles) over the period of 1 hour. The mixture was heated with vigorous stirring until all of the amine had dissolved. The solution was cooled to 10° and filtered. Any amine which had not been converted to the salt was again dissolved in hydrochloric acid, cooled, filtered, and combined with the original mother liquor. The solution was cooled to 0-5°, diazotized over a period of 20 minutes by addition of 9.5 g. of solid sodium nitrite (0.138 moles). The solution was stirred at 5-10° for 1 hour longer and filtered slowly into a solution of 29.2 g. of potassium ethyl xanthate (0.165 moles) and 60 g. of borax dissolved in 200 ml. of water at 60-70°. (It is necessary to add the diazonium solution slowly otherwise an explosive evolution of gas may ensue). The mixture was heated at 60-70° until evolution of gas ceased. The mixture was cooled and the oil which formed was separated from the

aqueous solution by ether extraction. The ethereal solution was washed once with dilute sodium hydroxide, twice with water, and dried over anhydrous sodium sulfate. The ether was removed and the dark oil remaining was added to 17.5 g. of potassium hydroxide (0.325 moles) dissolved in 300 ml. of 95% ethanol. The mixture was refluxed under an atmosphere of nitrogen until a test portion was completely soluble in water (about 2 hours). The solution was then mixed with an equal amount of water, poured into a separatory funnel which had previously been flushed with nitrogen. Benzyl chloride (19.5 g., 0.154 moles) was added and the mixture shaken vigorously for 10 minutes. The solution was kept alkaline to litmus by appropriate addition of dilute sodium hydroxide. The solution was extracted with ether, the ethereal solution washed with water and dried over anhydrous sodium sulfate. The ether was removed by distillation and the oil remaining was fractionally distilled under vacuum to yield 6.8 g. (19%) of 2-nitro-3-benzylmercaptotoluene, b.p. 90-100° (18 mm.), m.p. 50-52° uncorr.

Anal. Calculated for $C_{14}H_{13}O_2NS$: S, 12.32

Found: S, 12.38.

SUMMARY

4-Benzylmercaptoindole has been prepared via the Reissert indole synthesis. This involved preparation of 2-nitro-6-benzylmercaptotoluene from 2-nitro-6-bromotoluene. The benzylmercaptotoluene was then condensed with diethyl oxalate in the presence of potassium tertiary butoxide since sodium ethoxide, the base normally used for the Reissert synthesis, proved too weak, the resulting phenyl pyruvic acid was cyclized to the carboxyindole and decarboxylated with a copper chromite catalyst in refluxing quinoline. The 4-benzylmercaptoindole was debenzylated with sodium in liquid ammonia to yield a compound tentatively identified as 4-mercaptoindole.

2-Nitro-3-benzylmercaptotoluene was synthesized via diazotation and xanthation of 2-nitro-3-aminotoluene. However, the product could not be induced to condense with diethyl oxalate.

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